





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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60/112,544 16 December 1998 (16.12.98) US 60/164,651 10 November 1999 (10.11.99) US

(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

- (75) Inventors/Applicants (for US only): DUDLEY, David, Thomas [US/US]; 3700 Waters Road, Ann Arbor, MI 48103 (US). FLORY, Craig, Mason [US/US]; 3448 Pineview Drive West, Dexter, MI 48130 (US). SALTIEL, Alan, Robert [US/US]; 2002 Valley View Drive, Ann Arbor, MI 48105 (US).
- (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IÊ, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Without international search report and to be republished upon receipt of that report.

(54) Title: TREATMENT OF ARTHRITIS WITH MEK INHIBITORS

(57) Abstract

This invention provides a method for preventing and treating arthritis in a mammal suffering from arthritis and in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a MEK inhibitor, including a compound of Formula (I) and Formula (II).

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EE	Estonia	LR	Liberia	SG	Singapore		

PCT



INTERNATIONAL PRELIMINARY EXAMINATION R (PCT Article 36 and Rule 70)

Applicant's c	or agent's file reference	T				
		FOR FURTHER ACTION		ation of Transmittal of International Examination Report (Form PCT/IPEA/416)		
PD-5968-01-EDS Preliminary Ex			report (Form FOT//FE/416)			
	application No.	International filing date (day/month/	'year)	Priority date (day/month/year)		
PCT/US99	9/29783	15/12/1999	·	16/12/1998		
	International Patent Classification (IPC) or national classification and IPC A61K31/00					
Applicant						
	-LAMBERT COMPANY et	-1				
WARNER	-LAMBERT COMPANT et	aı.				
1. This int	ternational preliminary examil transmitted to the applicant a	nation report has been prepared coording to Article 36.	by this Inter	mational Preliminary Examining Authority		
2. This Ri	EPORT consists of a total of	8 sheets, including this cover she	eet.			
be	en amended and are the basi	d by ANNEXES, i.e. sheets of the is for this report and/or sheets co of the Administrative Instruction	ntaining rec	n, claims and/or drawings which have ctifications made before this Authority e PCT).		
These a	These annexes consist of a total of sheets.					
3. This rep						
11	☐ Priority					
Ш	Non-establishment of op	pinion with regard to novelty, inve	ntive step a	and industrial applicability		
IV	☐ Lack of unity of invention		•			
V	Reasoned statement und citations and explanation	der Article 35(2) with regard to no	ovelty, inven	ntive step or industrial applicability;		
VI	□ Certain documents cited	d .				
VII	Certain defects in the int	ternational application				
VIII	□ Certain observations on	the international application				

Date of submission of the demand

16/06/2000

14.12.2000

Name and mailing address of the international preliminary examining authority:

Date of completion of this report

4.12.2000

Authorized officer



European Patent Office D-80298 Munich

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

I. Basis of the report

1.	res the	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).): Description, pages:							
	1-8	1	as originally filed						
	Cla	ims, No.:							
	1-1	6	as originally filed						
2.			juage, all the elements marked above were available or furnished to this Authority in the international application was filed, unless otherwise indicated under this item.						
	The	ese elements were a	available or furnished to this Authority in the following language: , which is:						
		the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).							
		the language of publication of the international application (under Rule 48.3(b)).							
	translation furnished for the purposes of international preliminary examination (under Rule								
3.			leotide and/or amino acid sequence disclosed in the international application, the y examination was carried out on the basis of the sequence listing:						
		contained in the in	ternational application in written form.						
		filed together with	the international application in computer readable form.						
		☐ furnished subsequently to this Authority in computer readable form.							
		The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.							
		The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.							
4.	The	amendments have	resulted in the cancellation of:						
		the description,	pages:						
		the claims,	Nos.:						
		the drawings,	sheets:						
5.	☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):								

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/US99/29783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this

		report.)		9	Tames and the second to and armoxed to and
6.	Ado	litional observations, if n	ecessa	ry:	
III.	. Nor	n-establishment of opir	nion wit	th regard	I to novelty, inventive step and industrial applicability
		estions whether the clai e industrially applicable b			opears to be novel, to involve an inventive step (to be non-obvious), camined in respect of:
		the entire international	applicat	ion.	
	×	claims Nos. 1-16.			
be	caus	se:			
	☒				said claims Nos. 1-16 (industrial applicability) relate to the following n international preliminary examination (<i>specify</i>):
		the description, claims of that no meaningful opin			cate particular elements below) or said claims Nos. are so unclear ned (specify):
		the claims, or said claim could be formed.	ns Nos.	are so ir	nadequately supported by the description that no meaningful opinion
		no international search	report h	as been	established for the said claims Nos
2.	and				nation report cannot be carried out due to the failure of the nucleotid with the standard provided for in Annex C of the Administrative
		the written form has not	been fu	urnished (or does not comply with the standard.
		the computer readable t	orm ha	s not bee	n furnished or does not comply with the standard.
V.		soned statement unde tions and explanations			rith regard to novelty, inventive step or industrial applicability; ch statement
1.	State	ement			
	Nov	elty (N)	Yes: No:	Claims Claims	6-16 1-5
	Inve	ntive step (IS)	Yes: No:	Claims Claims	1-16
	Indu	strial applicability (IA)	Yes:	Claims	see section III

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International application No. PCT/US99/29783

No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

EXAMINATION REPORT - SEPARATE SHEET

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Prior Art: Reference is made to the following documents cited in the International 2. Search Report

D1: WO 99 61440 A

D2: WO 99 57101 A

D3: WO 99 01449 A

D4: J. BIOL. CHEM., vol. 273 (1998), pages 24832-24838

D5: J. PHARM. EXP. THERAP., vol. 284 (1998), pages 687-692

D6: J. OF IMMUNOLOGY, vol. 161 (1998), pages 467-473

D7: WO 98 37881 A: cited in the application

D8: BIOORG. MED. CHEM. LETT., vol. 8 (1998), pages 3335-3340

D9: WO 98 28292 A

D10: WO 96 00082 A

- 3. Novelty and Inventive Step (Article 33(2) and (3) PCT):
- Claims 1-5 relate to the treatment/prevention of arthritis comprising administering an 3.1 effective antiarthritic amount of a MEK inhibitor.

Documents D4-D6 and D8-D9, which disclose imidazole and indole derivatives, respectively, acting as p38-MAPK inhibitors for the treatment of arthritis, do not seem to anticipate the subject-matter of claims 1-5.

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Document D10, however, discloses the use of bromelain, which inhibits the phosphorylation of MAPK (p 31), for the treatment of rheumatoid arthritis (claim 15). thus anticipating the subject-matter of claims 1-5, which is therefore not novel.

Besides, taking into account that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis (cf. documents D4-D6, D8-D9), the choice to inhibit the "upstream" kinase does not seem to involve an inventive step.

3.2 Claims 6-14 and 15-16 relate to the treatment/prevention of arthritis using specific MEK inhibitors/compounds.

Documents D4-D6 and D8-D9, disclose imidazole and indole derivatives, respectively, as MAPK inhibitors for the treatment of arthritis, thus differing with respect to the compounds used. Accordingly, the subject-matter of said claims seems to be novel.

The problem to be solved by the current application can be regarded as to provide alternative compounds for the treatment of arthritis.

Taking into account that document D7 discloses the same compounds as MEK inhibitors (for the treatment of sceptic shock) and that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis, the subject-matter of claims 6-16 does not seem to be inventive.

4. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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International application No. PCT/US99/29783

EXAMINATION REPORT - SEPARATE SHEET

Re Section VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
D1: WO 99 61440 A	02.12.99	25.05.99	26.05.98
D2: WO 99 57101 A	11.11.99	28.04.99	05.05.98 and 02.03.99
D3: WO 99 01449 A	14.01.99	26.06.98	30.06.97

5. Document D1 could anticipate the novelty of claims 1-5 in the regional phase.

Re Section VII

Certain defects in the international application

- 6. On page 52, the name for example 207 seems to be wrong.
- 7. The chemical name of PD 199601 on page 77 in Table 3 seems to be missing.
- 8. The second concentration of PD 184352 in Table 4 on page 78 seems to be wrong.

Re Section VIII

Certain observations on the international application

- 9. Independent claim 1 (and dependent claims) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (MEK inhibitor) which merely amounts to a statement of the underlying problem. It is not clear which criterium (e.g., IC₅₀-test) has to be met for a compound to fall within the scope of the claim.
- 10. The parentheses in claim 6 for the definition of Z being hetero-cycloalkyl seem to be wrong.
- The sulfamoyl-substituted compounds of dependent claim 7 do not seem to fall within 11. the range of Formula I (claim 6).

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EXAMINATION REPORT - SEPARATE SHEET

- Claim 8 seems to be unclear ("or (k) or combinations of the above").
- 13. The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2ylmethoxy)-benzamide in claim 13 (p 98) seems to be wrong.
- The PD-number of the last compound in claim 14 is missing.
- 15. The embodiments of the invention "synthesis and synthetic intermediates" described on page 24, line 15, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- 16. The embodiments of the invention "thiobenzoic acid" described on page 47, examples 140-145, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- The vague statement "scope" of the specification used on page 35 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret it (PCT-Guidelines, III-4.3a).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



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PCT

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Alan, Robert [US/US]; 2002 Valley View Drive, Ann Arbor, MI 48105 (US).

- (21) International Application Number:
- (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

(81) Designated States (national): AE, AL, AU, BA, BB, BG,

BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID,

IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA,

(22) International Filing Date:

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- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; Tabor Road, Morris Plains, NJ 07950 (US).

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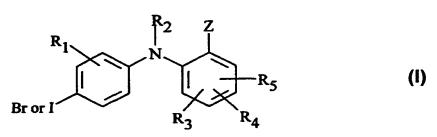
with international search report

US, UZ, VN, YU, ZA.

- (72) Inventors; and
- (75) Inventors/Applicants (for US only): DUDLEY, David, Thomas [US/US]; 3700 Waters Road, Ann Arbor, MI 48103 (US). FLORY, Craig, Mason [US/US]; 3448 Pineview Drive West, Dexter, MI 48130 (US). SALTIEL,
- (88) Date of publication of the international search report: 18 October 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF ARTHRITIS WITH MEK INHIBITORS



(57) Abstract: This invention provides a method for preventing and treating arthritis in a mammal suffering from arthritis and in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a MEK inhibitor, including a compound of Formula (I) and Formula (II).



Inte onal Application No PCT/US 99/29783

A. CLASSIF IPC 7	CATION OF SUBJECT A61K31/195 A61K31/495	A61K31/166	A61K31/13 A61K31/38	6 A61K31/41 A61K31/34	A61K31/445
According to	International Patent Class	sification (IPC) or to both	national classification	n and IPC	
B. FIELDS S					
Minimum doo IPC 7	cumentation searched (cl A61K	assification system follow	ved by classification	symbols)	
Documentati	on searched other than m	ninimum documentation to	o the extent that such	n documents are included in	the fields searched
Electronic da	ata base consulted during	the international search	(name of data base	and, where practical, search	n terms used)
· ·	THIS CONSIDERED TO	BE RELEVANT			
	ation of document, w	ith indication, where app	ropriate, of the relev	ant passages	Relevant to claim No.
Р		O A (SMITHKLI 1999 (1999-12 3		CO)	1-5
	11 November	 L A (F. HOFFM/ 1999 (1999-1 ine 14 - line 37-43	11-11)	E AG)	1-5
	14 January claims 1-0 page 20, l	9 A (NOVARTIS 1999 (1999-0) 5,8-11 ine 16 - line ine 14 -page	1-14) 21		1-5
		-	-/		
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Furt	her documents are listed i	n the continuation of box	C.	Patent family member	ers are listed in annex.
Special c	ategories of cited docume	nts:	*1		after the international filing date
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filing of "L" docume which	date ent which may throw doub is cited to establish the p	its on priority claim(s) or ublication date of another	. '	cannot be considered no involve an inventive step "document of particular relations."	evance; the claimed invention vel or cannot be considered to when the document is taken alone evance; the claimed invention
O docum other	n or other special reason ent referring to an oral dis means	closure, use, exhibition of	or	cannot be considered to document is combined w	involve an inventive step when the ith one or more other such docubeing obvious to a person skilled
	ent published prior to the than the priority date claim		ut	in the art. if document member of the	same patent family
Date of the	actual completion of the i	nternational search		Date of mailing of the inte	ernational search report
	April 2000			19/04/2000	
Name and	mailing address of the IS/ European Patent Of NL - 2280 HV Rijsv	fice, P.B. 5818 Patentiaa	n 2	Authorized officer	
		2040, Tx. 31 651 epo ni,		Siatou, E	

Into Jonal Application No
PCT/US 99/29783

100	Non DOCUMENTS CONSIDERED TO BE BELEVANT	FC1703 99729783
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38,	1-5
	18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	
Y	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1–5
Y	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1	1-5

Intic Jonal Application No
PCT/US 99/29783

		FC1/US 99/29/63
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21	1-5
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document	1-16
		·

...iernational application No.

PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box il Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

in. itional Application No PCT/US 99/29783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9961440 A	02-12-1999	NONE	
WO 9957101 A	11-11-1999	NONE	
WO 9901449 A	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
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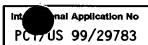
(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	(Form PCT/ISA/2	of Transmittal of International Search Report 20) as well as, where applicable, item 5 below.				
5968-01-EDS	ACTION					
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)				
PCT/US 99/29783	15/12/1999	16/12/1998				
Applicant						
WARNER-LAMBERT COMPANY et	al.					
This International Search Report has bee according to Article 18. A copy is being to	n prepared by this International Searching Aut ansmitted to the International Bureau.	nority and is transmitted to the applicant				
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	report.				
Basis of the report						
	international search was carried out on the bar less otherwise indicated under this item.	sis of the international application in the				
the international search w Authority (Rule 23.1(b)).	ras carried out on the basis of a translation of t	he international application furnished to this				
b. With regard to any nucleotide an was carried out on the basis of th		temational application, the international search				
1	onal application in written form.					
	emational application in computer readable for	n.				
	furnished subsequently to this Authority in written form.					
	o this Authority in computer readble form. Osequently furnished written sequence listing d	oes not go beyond the disclosure in the				
international application a	s filed has been furnished.					
the statement that the infe	ormation recorded in computer readable form i	s identical to the written sequence listing has been				
2. X Certain claims were fou	nd unsearchable (See Box I).					
3. Unity of invention is lac	king (see Box II).					
4. With regard to the title ,						
X the text is approved as su	ıbmitted by the applicant.					
the text has been establis	shed by this Authority to read as follows:					
5. With regard to the abstract,						
X the text is approved as su	ubmitted by the applicant.					
	shed, according to Rule 38.2(b), by this Authorical action of mailing of this international search rep					
6. The figure of the drawings to be pub	lished with the abstract is Figure No.					
as suggested by the appl		None of the figures.				
because the applicant fai						
because this figure better	characterizes the invention.					



hational application No.
PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
 X Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically: 3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
De la Character de la Carte de
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7-A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5

Patent family members are listed in annex.
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of mailing of the international search report 19/04/2000
19/04/2000
Authorized officer Siatou, E



Int nal Application No PC17 US 99/29783

Citation of document, with indication, where appropriate, of the relevant passages K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6	Relevant to claim No.
K. MIYAZAWA ET AL: "Regulation of Interleukin-6	
Interleukin-1-beta-induced Interleukin-6	1–5
Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	6.16
page 2483/, right-hand column, last paragraph 	6-16
J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
abstract page 690, right-hand column, line 7 - line 24	6-16
A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932	1-5
page 472, right-hand column, last paragraph	6-16
WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5
	18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract page 24837, right-hand column, last paragraph J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931 abstract page 690, right-hand column, line 7 - line 24 A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract page 472, right-hand column, last paragraph WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9 HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2



Int nal Application No PCT, JS 99/29783

		PC17-03 99/29/63
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	<u> </u>
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
(WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19	1-5
	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21	1-5
	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document	1-16

INTERNATIONAL SEARCH REPORT Information patent family members

Int mal Application No PCT, US 99/29783

					0., 00	33, 23, 33
Patent document cited in search repo	rt	Publication date		Patent family member(s)		Publication date
WO 9961440	Α	02-12-1999	NONE	•		
WO 9957101	Α	11-11-1999	NONE			
WO 9901449	Α	14-01-1999	AU	8801598		25-01-1999
			NO ZA	996429 9805656		23-12-1999 30-12-1998
W0 9837881	A	03-09-1998	AU	5610398		18-09-1998
			ZA	9801578	Α	02-09-1998
W0 9828292	Α	02-07-1998	NONE			
W0 9600082	Α	04-01-1996	AU	2749395		19-01-1996
			CA	2193654		04-01-1996
			CN	1151119		04-06-1997
			EP	0766565		09-04-1997
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			NO	965564		24-02-1998 24-02-1997
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			AU	690400		23-04-1998
			AU	4245696		14-08-1996
			CA	2208075		01-08-1996
			DE	69510696		12-08-1999
			DE	69510696		23-12-1999
			EP	0805807		12-11-1997
			GR	3031295		31-12-1999
			JP	10512878		08-12-1998
			NZ	297320		28-05-1999
			WO	9622985		01-08-1996
			ZA	9600528	A	15-08-1996



PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification of	f Transmittal of International Search Report
5968-01-EDS	ACTION (Form PCT/ISA/2	20) as well as, where applicable, item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 99/29783	15/12/1999	16/12/1998
Applicant		
WARNER-LAMBERT COMPANY et	al.	
This International Search Report has bee according to Article 18. A copy is being to	n prepared by this International Searching Autr ansmitted to the International Bureau.	nority and is transmitted to the applicant
This International Search Report consists	of a total of _ 5 sheets.	
· · · · · · · · · · · · · · · · · · ·	a copy of each prior art document cited in this	report.
Basis of the report With regard to the language, the	interpolicant approximation and an the base	in adalah saharan kanada saharan kanada saharan kanada saharan kanada saharan kanada saharan kanada saharan ka
language in which it was filed, un	international search was carried out on the bas less otherwise indicated under this item.	is of the international application in the
the international search w Authority (Rule 23.1(b)).	vas carried out on the basis of a translation of th	ne international application furnished to this
 With regard to any nucleotide an was carried out on the basis of th 	d/or amino acid sequence disclosed in the in	ternational application, the international search
	e sequence listing : onal application in written form.	
	ernational application in computer readable form	1.
furnished subsequently to	this Authority in written form.	
furnished subsequently to	this Authority in computer readble form.	
the statement that the sub international application a	osequently furnished written sequence listing do s filed has been furnished.	bes not go beyond the disclosure in the
the statement that the info furnished	ormation recorded in computer readable form is	identical to the written sequence listing has been
2. X Certain claims were fou	nd unsearchable (See Box I).	
3. Unity of invention is lac		
4 1979		
 With regard to the title, the text is approved as su 	hoolikaal kuulka aaalisaat	
and text has been establis	hed by this Authority to read as follows:	
5. With regard to the abstract,		
X the text is approved as su		
the text has been establis within one month from the	hed, according to Rule 38.2(b), by this Authorite date of mailing of this international search repe	y as it appears in Box III. The applicant may,
6. The figure of the drawings to be publ		st, submit comments to the realismy.
as suggested by the appli		None of the figures.
because the applicant faile		
	characterizes the invention.	



rnational application No.

PCT/US 99/29783

Box I Observations where certain claims were found unsearch	hable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of cert	ain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 1-16 because they relate to subject matter not required to be searched to Remark: Although claims 1-16 are directed to a method of tre body, the search has been carri effects of the compound/composi	eatment of the human/animal ed out and based on the alleged
Claims Nos.: because they relate to parts of the International Application that do an extent that no meaningful International Search can be carried or	not comply with the prescribed requirements to such ut, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance.	nce with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Conti	nuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this intern	ational application, as follows:
As all required additional search fees were timely paid by the applic searchable claims.	cant, this International Search Report covers all
2. As all searchable claims could be searched without effort justifying of any additional fee.	an additional fee, this Authority did not invite payment
3. As only some of the required additional search fees were timely pai covers only those claims for which fees were paid, specifically claim	id by the applicant, this International Search Report ns Nos.:
4. No required additional search fees were timely paid by the applican restricted to the invention first mentioned in the claims; it is covered	it. Consequently, this International Search Report is by claims Nos.:
	search fees were accompanied by the applicant's protest. ompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Citation of document, with indication, where appropriate, of the relevant passages	
	Relevant to claim No.
WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5
WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5
	2 December 1999 (1999-12-02) claims 1-8 WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43 WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14

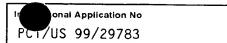
X Further documents are listed in the continuation of box C.	Y Patent family members are listed in annex.
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2000	19/04/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk	Authorized officer
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E





C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Υ	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Υ	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5





		PC1/US 99	7/29/03
C.(Continu Category °	Citation of document, with indication where appropriate of the relevant		15.
Jalegory 1	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
(WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19		1-5
	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21		1-5
	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document		1-16
	-		

n on patent family members

ional Application No PCT/US 99/29783

Patent document cited in search repo		Publication date	Patent family member(s)	Publication date
WO 9961440	Α	02-12-1999	NONE	
W0 9957101	Α	11-11-1999	NONE	
WO 9901449	Α	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
W0 9837881	Α	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998
WO 9828292	Α	02-07-1998	NONE	
W0 9600082	A	04-01-1996	AU 2749395 A CA 2193654 A CN 1151119 A EP 0766565 A FI 965204 A JP 10502073 T NO 965564 A	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
US 5525625	A	11-06-1996	AT 181913 T AU 690400 B AU 4245696 A CA 2208075 A DE 69510696 D DE 69510696 T EP 0805807 A GR 3031295 T JP 10512878 T NZ 297320 A WO 9622985 A ZA 9600528 A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996



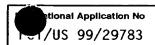
(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS		of Transmittal of International Search Report 220) as well as, where applicable, item 5 below.			
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)			
PCT/US 99/29783	15/12/1999	16/12/1998			
Applicant WARNER-LAMBERT COMPANY et	al.				
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching Autansmitted to the International Bureau.	thority and is transmitted to the applicant			
This International Search Report consists It is also accompanied by	of a total of5 sheets. a copy of each prior art document cited in this	s report.			
Basis of the report					
	international search was carried out on the ba ess otherwise indicated under this item.	isis of the international application in the			
the international search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of	the international application furnished to this			
was carried out on the basis of the		nternational application, the international search			
	rnational application in computer readable for	m.			
=	this Authority in written form.				
	this Authority in computer readble form.				
the statement that the sub	osequently furnished written sequence listing of stiled has been furnished.	does not go beyond the disclosure in the			
the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished					
2. X Certain claims were fou	nd unsearchable (See Box I).				
3. Unity of invention is lac	king (see Box II).				
4. With regard to the title,					
the text is approved as su	bmitted by the applicant.				
the text has been establis	hed by this Authority to read as follows:				
5. With regard to the abstract ,					
TX the text is approved as su	bmitted by the applicant.				
the text is approved as submitted by the applicant. the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.					
6. The figure of the drawings to be publ	ished with the abstract is Figure No.				
as suggested by the appli	cant.	None of the figures.			
because the applicant fail	ed to suggest a figure.				
because this figure better	characterizes the invention.				



ernational application No.
PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
 X Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



a. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED	10 DE HELEVARIT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х,Р	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14 -/	1-5

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search 5 April 2000	Date of mailing of the international search report $19/04/2000$

Authorized officer

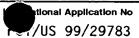
Siatou, E

Form PCT/ISA/210 (second sheet) (July 1992)

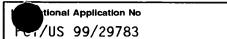
1

Name and mailing address of the ISA

Ruropean Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016



		197/US 99/29/83
C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XPO02134930	1-5
Υ	abstract page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, ypno2134031	1-5
Y	XP002134931 abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5



		Te1/03 9	9/29/83
(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		
ategory °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
(WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19		1-5
(WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21		1-5
	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document		1-16
	•		
		·	:

on on patent family members

tional Application No

	itent document I in search repor	t	Publication date		atent family nember(s)		Publication date
WO	9961440	Α	02-12-1999	NONE			<u> </u>
WO	9957101	Α	11-11-1999	NONE			
WO	9901449	A	14-01-1999	AU	8801598		25-01-1999
				NO	996429		23-12-1999
				ZA	9805656	Α	30-12-1998
MO	9837881	Α	03-09-1998	AU	5610398		18-09-1998
				ZA	9801578	Α	02-09-1998
WO	9828292	A	02-07-1998	NONE			
WO	9600082	Α	04-01-1996	AU	2749395	A	19-01-1996
				CA	2193654	Α	04-01-1996
				CN	1151119	Α	04-06-1997
				EP	0766565		09-04-1997
				FΙ	965204	Α	21-02-1997
				JP		T	24-02-1998
				NO	965564	Α	24-02-1997
US	5525625	Α	11-06-1996	AT	181913	T	15-07-1999
				AU	690400		23-04-1998
				AU	4245696		14-08-1996
				CA	2208075		01-08-1996
				DE	69510696		12-08-1999
				DE		T	23-12 - 1999
				EP	0805807	Α	12-11-1997
				GR	3031295	T	31-12-1999
				JP	10512878	T	08-12-1998
				ΝZ	297320		28-05-1999
				WO		Α	01-08-1996
				ZA	9600528	Α	15-08-1996

P. ENT COOPERATION TREA.

	From the INTERNATIONAL BUREAU				
PCT	То:				
NOTIFICATION OF ELECTION (PCT Rule 61.2)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE				
Date of mailing (day/month/year) 16 August 2000 (16.08.00)	in its capacity as elected Office				
International application No. PCT/US99/29783 International filing date (day/month/year)	Applicant's or agent's file reference 5968-01-EDS Priority date (day/month/year)				
15 December 1999 (15.12.99)	16 December 1998 (16.12.98)				
Applicant DUDLEY, David, Thomas et al					
The designated Office is hereby notified of its election made in the demand filed with the International Preliminary 16 June 2000 (in a notice effecting later election filed with the Intern	r Examining Authority on: (16.06.00)				
2. The election X was was not was not made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).					
The International Rureau of WIPO	Authorized officer				

Form PCT/IB/331 (July 1992)

Facsimile No.: (41-22) 740.14.35

34, chemin des Colombettes

1211 Geneva 20, Switzerland

Christelle Croci

Telephone No.: (41-22) 338.83.38

- Rose Armstrong Charles Ashbrook

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

WARNER-LAMBERT COMPANY et al.

MANSMANN, I. Patentwesen NOTIFICATION OF TRANSMITTAL OF Warner-Lambert Company Legal Division THE INTERNATIONAL PRELIMINARY Eing.: 15. Dez. 2000 c/o Gödecke AG, Patents **EXAMINATION REPORT** Mooswaldallee 1 (PCT Rule 71.1) D-79090 Freiburg ALLEMAGNE Date of mailing 14.12.2000 (day/month/year) والمراب المساهدي ماراد Applicant's or agent's file reference IMPORTANT NOTIFICATION PD-5968-01-EDS Priority date (day/month/year) International filing date (day/month/year) International application No. 16/12/1998 15/12/1999 PCT/US99/29783 **Applicant**

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Th

Name and mailing address of the IPEA/

Authorized officer

European Patent Office D-80298 Munich

Hundt, D

Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465

Tel.+49 89

and the second





PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD-5968-01-EDS	FOR FURTHER AC	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
	International filing date (d	day/month/year) Priority date (day/month/year)
International application No.	15/12/1999	16/12/1998
PCT/US99/29783		
International Patent Classification (IPC) o A61K31/00	r national classification and IPC	• ·
	6 4, % **	
Applicant	as "	
WARNER-LAMBERT COMPANY	et al.	
This international preliminary exand is transmitted to the application. This REPORT consists of a total.	nt according to Article 36. I of 8 sheets, including this	· 18
heen amended and are the	basis for this report and/or n 607 of the Administrative	eets of the description, claims and/or drawings which have sheets containing rectifications made before this Authority Instructions under the PCT).
3. This report contains indications		ns:
I 🖾 Basis of the report	المحمولية المالي المالية المال المالية المالية المالي	e
II □ Priority		.**
		velty, inventive step and industrial applicability
IV 🔲 Lack of unity of inve	ention	
V 🖾 Reasoned statemer	nt under Article 35(2) with renations suporting such state	egard to novelty, inventive step or industrial applicability; ement
	cited	
	ne international application	
	s on the International applic	cation
	in describeration in the second secon	
Date of submission of the demand	y valendarija	Date of completion of this report
16/06/2000	ng co	14.12.2000
Name and mailing address of the interna	ional	Authorized officer
preliminary examining authority: European Patent Office		
D-80298 Munich		Winger, R
Tel. +49 89 2399 - 0 Tx: 52 Fax: +49 89 2399 - 4465	3656 epmu d	Telephone No. +49 89 2399 8129

Form PCT/IPEA/409 (cover sheet) (January 1994)

Andry - Allin



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

		ia or allo roport		
1.	resp the i	onse to an invitation	wn on the basis of (substitute sheets which have been furnished to the receiving Office under Article 14 are referred to in this report as "originally filed" and are not annexed to not contain amendments (Rules 70.16 and 70.17).):	in >
	1-81		s originally filed	
	1-01	ı a		
	Clai	ms, No.:		
			s originally filed	
	1-16) H	s originally med	
			and define the second of	
^	\A/aL	regard to the length	age, all the elements marked above were available or furnished to this Authority in the	
۷.	land	regard to the langu Juage in which the inf	emational application was filed, unless otherwise indicated under this item.	
	_			
	The	se elements were av	ailable or furnished to this Authority In the following language: , which is:	
		the language of a tri	inslation furnished for the purposes of the international search (under Rule 23.1(b)).	
			ication of the International application (under Rule 48.3(b)).	
	_	• • •	instation furnished for the purposes of international preliminary examination (under Rul	A
		55.2 and/or 55.3).	Instation furnished for the purposes of international profilminary oxidination (and of the	
		-		
3.	With	regard to any nucle	otide and/or amino acid sequence disclosed in the international application, the examination was carried out on the basis of the sequence listing:	
	Intel	mational preliminary	3Xammation was carried out on the basis of the sequence nothing.	
		contained in the inte	mational application in written form.	
			e international application in computer readable form.	•
			ntly to this Authority in written form.	
			ntly to this Authority in computer readable form.	
		•	ne subsequently furnished written sequence listing does not go beyond the disclosure i	n
		the international app	lication as filed has been furnished.	
			he information recorded in computer readable form is identical to the written sequence	
		listing has been furn	shed.	
4.	The	amendments have r	esulted in the cancellation of:	
			e de Maria de la companya della companya della companya de la companya della comp	
		the description,	pages:	
		the claims,	Nos.:	
		the drawings,	sheets:	
_	_		and the bank of the amondments had not been made along they been been	
5.			established as if (some of) the amendments had not been made, since they have been yond the disclosure as filed (Rule 70.2(c)):	•





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

					4 · · · · · · · · · · · · · · · · · · ·
6.	Add	litional observations, if ne	ecessan	/ :	
111.	Nor	n-establishment of opin	ion witi	n regard	to novelty, inventive step and industrial applicability
Th	e an		ned inve	ention app	pears to be novel, to involve an inventive step (to be non-obvious),
		the entire international a	applicati	on.	
	×	claims Nos. 1-16.			
be	caus	se:		<u>د</u>	na 1944 Greek I. Greek Brown (1944)
	Ø	the said international ap subject matter which do see separate sheet	oplication oes not r	n, or the sequire an	said claims Nos. 1-16 (industrial applicability) relate to the following international preliminary examination (<i>specify</i>):
		the description, claims that no meaningful opin	or drawl ion coul	ngs (<i>Indid</i> d be form	cate particular elements below) or said claims Nos. are so unclear ned (specify):
	0	the claims, or said clain could be formed.	ns Nos.	are so in	nadequately supported by the description that no meaningful opinion
		no international search	report h	as been	established for the said claims Nos
2.	and	neaningful international p Nor amino acid sequence tructions:	relimina e listing	ry exami to comply	nation report cannot be carried out due to the failure of the nucleotid y with the standard provided for in Annex C of the Administrative
	_	the written form has no	t hoon fi	irnished (or does not comply with the standard.
					en furnished or does not comply with the standard.
	_				
V.	Re	asoned statement unde ations and explanations	er Articles s suppo	e 35(2) w rting suc	vith regard to novelty, inventive step or industrial applicability; ch statement
1.	Sta	tement			
	No	velty (N)	Yes: No:	Claims Claims	
	Inv	entive step (IS)	Yes: No:	Claims Claims	1-16 ⁷
	Ind	lustrial applicability (IA)	Yes:	Claims	see section III





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and/or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

INTERNATIONAL PRELIMINARY

EXAMINATION REPORT - SEPARATE SHEET

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. <u>Prior Art:</u> Reference is made to the following documents cited in the International Search Report

D1: WO 99 61440 A

D2: WO 99 57101 A

D3: WO 99 01449 A

D4: J. BIOL. CHEM., vol. 273 (1998), pages 24832-24838

D5: J. PHARM. EXP. THERAP., vol. 284 (1998), pages 687-692

D6: J. OF IMMUNOLOGY, vol. 161 (1998), pages 467-473

D7: WO 98 37881 A: cited in the application

D8: BIOORG. MED. CHEM. LETT., vol. 8 (1998), pages 3335-3340

D9: WO 98 28292 A D10: WO 96 00082 A

3. Novelty and Inventive Step (Article 33(2) and (3) PCT):

3.1 Claims 1-5 relate to the treatment/prevention of arthritis comprising administering an effective antiarthritic amount of a MEK inhibitor.

Documents D4-D6 and D8-D9, which disclose imidazole and indole derivatives, respectively, acting as p38-MAPK inhibitors for the treatment of arthritis, do not seem to anticipate the subject-matter of claims 1-5.





INTERNATIONAL PRELIMINARY Inter EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/US99/29783

Document D10, however, discloses the use of bromelain, which inhibits the phosphorylation of MAPK (p 31), for the treatment of rheumatoid arthritis (claim 15), thus anticipating the subject-matter of claims 1-5, which is therefore not novel.

Besides, taking into account that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis (cf. documents D4-D6, D8-D9), the choice to inhibit the "upstream" kinase does not seem to involve an inventive step.

3.2 Claims 6-14 and 15-16 relate to the treatment/prevention of arthritis using specific MEK inhibitors/compounds.

Documents D4-D6 and D8-D9, disclose imidazole and indole derivatives, respectively, as MAPK inhibitors for the treatment of arthritis, thus differing with respect to the compounds used. Accordingly, the subject-matter of said claims seems to be novel.

The problem to be solved by the current application can be regarded as to provide alternative compounds for the treatment of arthritis.

Taking into account that document D7 discloses the same compounds as MEK inhibitors (for the treatment of sceptic shock) and that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis, the subject-matter of claims 6-16 does not seem to be inventive.

4. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.



INTERNATIONAL PRELIMINARY

International application No. PCT/US99/29783

EXAMINATION REPORT - SEPARATE SHEET

Re Section VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
D1: WO 99 61440 A	02.12.99	25.05.99	26.05.98
D2: WO 99 57101 A	11.11.99	28.04.99	05.05.98 and 02.03.99
D3: WO 99 01449 A	14.01.99	26.06.98	30.06.97

Document D1 could anticipate the novelty of claims 1-5 in the regional phase. 5.

Re Section VII

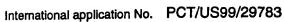
Certain defects in the international application

- On page 52, the name for example 207 seems to be wrong. 6.
- The chemical name of PD 199601 on page 77 in Table 3 seems to be missing. 7.
- The second concentration of PD 184352 in Table 4 on page 78 seems to be wrong. 8.

Re Section VIII

Certain observations on the international application

- Independent claim 1 (and dependent claims) do not meet the requirements of Article 9. 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (MEK inhibitor) which merely amounts to a statement of the underlying problem. It is not clear which criterium (e.g., IC_{50} -test) has to be met for a compound to fall within the scope of the claim.
- 10. The parentheses in claim 6 for the definition of Z being hetero-cycloalkyl seem to be wrong.
- 11. The sulfamoyl-substituted compounds of dependent claim 7 do not seem to fall within the range of Formula I (claim 6).





INTERNATIONAL PRELIMINARY Inter EXAMINATION REPORT - SEPARATE SHEET

- 12. Claim 8 seems to be unclear ("or (k) or combinations of the above").
- 13. The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide in claim 13 (p 98) seems to be wrong.
- 14. The PD-number of the last compound in claim 14 is missing.
- 15. The embodiments of the invention "synthesis and synthetic intermediates" described on page 24, line 15, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- 16. The embodiments of the invention "thiobenzoic acid" described on page 47, examples 140-145, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- 17. The vague statement "scope" of the specification used on page 35 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret it (PCT-Guidelines, III-4.3a).

PATENT COOPERATION TR

R ARMSTRONG

From the INTERNATIONAL SEARCHING AUTHORITY	PCT
UNITED STATES OF AMERICA	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION APR 2 4 2000 (PCT Rule 44.1) PATENT DEPT.
	Date of mailing (day/month/year) 19/04/2000
Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 99/ 29783	International filing date (day/month/year) 15/12/1999
Applicant WARNER-LAMBERT COMPANY et al.	
1. X The applicant is hereby notified that the International Search Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claim When? The time limit for filing such amendments is norma International Search Report; however, for more de Where? Directly to the International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41–22) 740.14.35 For more detailed instructions, see the notes on the accordance of the applicant is hereby notified that no International Search Article 17(2)(a) to that effect is transmitted herewith.	as of the International Application (see Rule 46): ally 2 months from the date of transmittal of the stails, see the notes on the accompanying sheet.
With regard to the protest against payment of (an) addition the protest together with the decision thereon has been	nal fee(s) under Rule 40.2, the applicant is notified that: n transmitted to the International Bureau together with the test and the decision thereon to the designated Offices.
no decision has been made yet on the protest; the app	vicant will be notified as soon as a decision is made.
4. Further action(s): The applicant is reminded of the following: Shortly after 18 months from the priority date, the international applicant wishes to avoid or postpone publication, a notice priority claim, must reach the International Bureau as provided completion of the technical preparations for international publics. Within 19 months from the priority date, a demand for internation wishes to postpone the entry into the national phase until 30 months from the priority date, the applicant must perforberor all designated Offices which have not been elected in the priority date or could not be elected because they are not bound.	of withdrawal of the international application, or of the in Rules 90bis.1 and 90bis.3, respectively, before the action. all preliminary examination must be filed if the applicant with from the priority date (in some Offices even later). The prescribed acts for entry into the national phase a demand or in a later election within 19 months from the

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Name and mailing address of the International Searching Authority

Authorized officer

Renate Jordan

Form PCT/ISA/220 (July 1998)

Express Mail No.EK651646072US PD-5968-01-SMH



These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication. (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been its filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Notes to Form PCT/ISA/220 (first sheet) (January 1994)



The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed:
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
 "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;
 claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- (Where originally there were 15 claims and after amendment of all claims there are 11): "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added. or
 Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged.
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46:4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19; a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

Notes to Form PCT/ISA/220 (second sheet) (January 1994)



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER see Notification of (Form PCT/ISA/2	See Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.				
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)				
PCT/US 99/29783	15/12/1999	16/12/1998				
Applicant	13/12/1999	10/12/1998				
WARNER-LAMBERT COMPANY et	al.					
according to Article 18. A copy is being to This International Search Report consists		,				
4 Balandhaman						
Basis of the report With regard to the language, the language in which it was filed, units to the language.	international search was carried out on the ba- less otherwise indicated under this item.	sis of the international application in the				
the international search w Authority (Rule 23.1(b)).	vas carried out on the basis of a translation of t	ne international application furnished to this				
was carried out on the basis of the contained in the internation filed together with the internation furnished subsequently to the statement that the sul international application a	e sequence listing: onal application in written form. emational application in computer readable form o this Authority in written form. o this Authority in computer readble form. because it is a computer to the computer readble form. because it is a computer readble form.					
\simeq	ind unsearchable (See Box I).					
3. Unity of invention is lac	king (see Box II).					
4. With regard to the title,						
X the text is approved as su	ibmitted by the applicant.					
the text has been establis	shed by this Authority to read as follows:	•				
within one month from the	shed, according to Rule 38.2(b), by this Authorities date of mailing of this international search rep	y as it appears in Box III. The applicant may, ort, submit comments to this Authority.				
6. The figure of the drawings to be publicated by the application	·	None of the figures.				
as suggested by the applicant fail						
	characterizes the invention.					



International application No.

PCT/US 99/29783

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	emational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

International Application No PCT/US 99/29783



A CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1–5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents: A' document defining the general state of the art which is not considered to be of particular relevance E' sarlier document but published on or after the international filling date L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) O' document referring to an oral disclosure, use, exhibition or other means P' document published prior to the international filling date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search 5 April 2000	Date of mailing of the international search report 19/04/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E

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International Application No PCT/US 99/29783

100-41	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	·	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages	1-5
	24832-24838, XP002134930 abstract	
Y	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Υ	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23,	1-5
	1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1	
	page 3337; table 2	

International Application No PCT/US 99/29783

- 12	<u>, </u>	PC1/US 99/29/83
	ntion) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25	1-5
A	page 11, line 21 US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document	1–16
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	-	
	ů.	

Information on patent family members

International Application No PCT/US 99/29783

	document earch report		Publication date		Patent family member(s)		Publication date
WO 99	61440	A	02-12-1999	NONE			
WO 99	57101	A	11-11-1999	NONE		·	
WO 99	01449	A	14-01-1999	AU	8801598		25-01-1999
				NO	996429		23-12-1999
				ZA	9805656	Α	30-12-1998
WO 98	37881	Α	03-09-1998	AU	5610398		18-09-1998
				ZA	9801578	A	02-09-1998
WO 98	28292	A	02-07-1998	NONE	·		
WO 96	00082	Α	04-01-1996	AU	2749395	Α	19-01-1996
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				EP	0766565		09-04-1997
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				NO	965564	A 	24-02-1997
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				AU		В	23-04-1998
				AU		A	14-08-1996
				CA		Α	01-08-1996
				DE		D	12-08-1999
				DE		T ·	23-12-1999
	•			EP		A	12-11-1997
				GR		<u>T</u>	31-12-1999
				JP		Ţ	08-12-1998
				NZ		A	28-05-1999
				WO		A	01-08-1996
				ZA	9600528	A	15-08-1996